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Discussion

Dr John S. Ikonomidis *(Charleston, SC).* Drs Burdon and Fullerton, I have no relationships to disclose with regard to this discussion. I thank Ross Bremner and the Western Thoracic Surgical Association for the opportunity to discuss this presentation today, and I rise to congratulate Drs Smith and Reece and the University of Colorado group for a really compelling characterization of this novel and interesting spinal cord protection phenomenon that we are really just starting to understand.

Dr Smith, I have a couple of comments and questions. I would like you to answer each question as I give it.

First, at first glance at this data, I am astounded that 5 minutes of normothermic ischemia caused uniform paralysis in every untreated animal studied. This is a devastating amount of damage that certainly would not be expected to occur in a similar clinical scenario in human beings, so I wonder whether you could comment on any potential anatomic or vascular-related differences between the murine model and human anatomy that could impede the extrapolation of these results to human patients into the clinical setting.

Dr Smith. Absolutely. Thank you for your kind comments. We feel that the most important thing is that the functional injury that we observe after aortic occlusion is very similar to what is seen clinically in human patients. The spinal cord anatomy and vasculature of a mouse is actually very similar to those of human beings, more than other animal models that have been used. Finally, the metabolic rate of a mouse is so much faster than that of a human being that you might actually expect that very short ischemic times such as those we used to have a much more pronounced effect.

Dr Ikonomidis. Thank you. Some logistic issues related to erythropoietin. How did you arrive at the timing and dosage of erythropoietin used in this study?

Dr Smith. We looked at the other literature, on the brain, and there have been many studies of the brain that outline different timing of administration and dosing, and we chose from there. In addition, we do not know the optimal timing or dosage, and we are doing further studies now to try to figure that out.

Dr Ikonomidis. How much does this cost in a mouse, and if you were to extrapolate that dose to human beings, how much would it cost if we were to use this clinically?

Dr Smith. I have not broken down the cost for a mouse. If you extrapolate the dose we used to a human dose, it would be about 120 unit/kg, so that would be about $200 to $300 per dose.

Dr Ikonomidis. It occurs to me that a single dose of erythropoietin, given the timing of this study, probably would not cause significant hematopoietic effects and is probably pretty benign. So in light of what we know already about it, should we start doing this in every case every time we do a descending thoracic replacement or thoracoabdominal? What is the harm in not giving it?

Dr Smith. I think that we need to further elucidate the mechanisms before we move into human trials, but because of the safety profile of erythropoietin and in the general population much less the aortic surgical population, I think it is very promising for treating every patient in the future.

Dr Ikonomidis. Your answer to that question is a good segue to the next one. There is relatively little literature on this subject, but the literature that is available shows this effect quite uniformly, so I think that it is reasonable to say that it really exists, and I think it is time to move forward and really start hammering out mechanisms. Your HIF1α data were not particularly compelling, but there are a variety of other potential mechanisms. These include anti-inflammatory effects, anti-apoptotic effects, modulation of oxidative stress, neurohormonal modulation of vascular tone, and even increased phosphorylation of certain upstream protective transcription factors, such as CREB. Are you leaning toward any of these particular mechanisms, or do you have a different mechanism in mind? How do you plan to study that?

Dr Smith. As you mentioned, there are several possible mechanisms that may be responsible for this effect. Although we did not observe a change in HIF1α at 48 hours, we still believe that it may be responsible, so we would like to look at and are looking at different time points to see whether we can show different expression after erythropoietin administration.

With respect to other mechanisms that may be involved, we are also looking at cytokine expression as a function of time after ischemia and reperfusion to see whether we can determine the important proinflammatory and anti-inflammatory cytokines that are responsible for the injury. Also, as I mentioned briefly, there are erythropoietin derivatives that do not have any hematopoietic effect but do have a cytoprotective effect, so we are using these to try to tease out the actual neuroprotective effects of these drugs.

Dr Jeffrey Gaca *(Durham, NC).* We often do these operations under hypothermia. Do you think that maybe you could reproduce this experiment under hypothermia and get different results, maybe even better results? A lot of times we don't do them under normothermia now.

Dr Smith. Absolutely, that is a great question. I think that if we did these experiments under hypothermic conditions, we might see even more neuroprotection. We do not know that for sure, because we have only done this under normothermia, but that would be a reasonable thing to try because that is what is done clinically.